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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,194	09/23/2004	Ramon Alemany Bonastre	16596-049US1	7846

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,194	BONASTRE ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050224*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

As per the preliminary amendment filed 9/24/05, pages 24a, 24b, 24c, and Figures 7-9 have been cancelled, and original page 8 and lines 1-24 of page 9 of the specification have been deleted.

Specification

The disclosure is objected to because of the following informalities. The deletion of page 8 and lines 1-23 of page 9, with the insertion of pages 8a, 9a, and 10a is confusing in that it is not clear from the record which order pages 8a, 9a, 10a, the remainder of page 9, and original page 10 are to appear. The confusion here is evident from the published application, US 2006/0233753, in ¶¶ 0008-0022. The order in which these pages has been published is page 8a, 9a, 10, 10a, and 11. As can be seen from the comments inserted by the printer in ¶¶ 0017, 0020, and 0021, this otherwise logical order of pages does not make sense. The remainder of page 9 was omitted, but logically might have been placed between pages 8a and 9a, where it also would have made no sense. The electronic file has pages the following order of pages: 8, 8a, 9, 9a, 10, 10a, 11. It appears that inserted pages 8a, 9a, and 10a should have been inserted in place of original page 8 and lines 1-23 of page 9, based upon the content of pages 8a-10a and the deleted text. However, there is nothing on the record to indicate that this is so. Appropriate correction is required.

In order to correct this problem, the amendment must conform to the requirements of 37 CFR 1.121. If, as the examiner surmises, the order should be pages 8a, 9a, 10a, lines 24-29 of original page 9, then original pages 10 and 11, the following would correct the problem and

comply with 37 CFR 1.121. Instructions to replace original pages 8-10, 8a, 9a, and 10a with one block of text that contains the following in order:

1) the text of pages 8a, 9a, and 10a;

2) the text of lines 24-29 of original page 9; and finally

3) the text of original page 10.

The only underlining or strikethrough appearing in this text should be to indicate new changes to the originally filed text on these pages (see the following objection to the specification).

The amendment filed 10/22/2003 during examination of PCT/ES03/00140 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows. Each of the paragraphs of pages 8a, 9a, and 10a, beginning with the second paragraph of page 8a, contain the phase "use of an adenovirus <u>for the production of a pharmaceutical composition</u> for the treatment of cancer" (emphasis added), which constitute new matter added to the original specification filed 3/25/2003. This phrase replaced the phrase "use of an adenovirus". This is new matter because the newly added phrase places no restrictions on how the adenovirus is used to produce the pharmaceutical composition, and more importantly, what the pharmaceutical composition actually is. There is no literal support for the added phrase in the original specification, nor any implied support for the phrase as broadly as it is written. The original specification implicitly supports a pharmaceutical composition comprising the adenovirus with defective VAI and VAII genes for the treatment of cancer. There is no indication in the original application that a method

of making a composition was considered part of the invention, or that the composition made was anything other than a composition comprising an adenovirus having defective VA genes. In addition, page 10a includes a new paragraph for which there was no counterpart in original pages 8 and 9, where the adenovirus is dl331. This prior art adenovirus does not, as implied by the first two paragraphs of page 8a, have defective VAI and VAII genes. It is an hAd5 strain with has a defective VAI gene, due to the dl331 mutation, but not a defective VAII gene, i.e. a functional wild type VAII gene is present.

Applicant is required to cancel the new matter in the reply to this Office Action. Changes to the originally presented text of pages 8a, 9a, and 10a should be included within the replacement text for pages 8a, 9a, 10a, 9, and 10 using underlining and strikethrough to show the new changes, as discussed in the preceding objection.

The last paragraph of page 9a also has no counterpart in the original specification. However, embodiments where the adenovirus is hAd5 were implicitly and explicitly described elsewhere in the specification (e.g. pages 16-18, and Figure 2).

Claim Objections

Claims 9 and 11 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 1, from which claims 9 and 11 depend, requires that there be a defective VAI and VAII gene. Claim 9 includes subject matter outside the scope of claim 1, and claim 11 is directed

to subject matter wholly outside the scope of claim 1. In order for there to be a defective VAI gene and a defective VAII gene, the starting adenovirus must first have had VAI and VAII genes. As disclosed in the specification, hAd of subgroups A and F and some of subgroup B have a single VA gene, i.e. these human adenoviruses do not have VAI and VAII genes. Specifically, these include serotypes 11, 12, 14, 18, 31, 34, 35, 40 and 41 (see Table 2 of Ma et al., J. Virol. 70: 5083-5099, 1996). Claim 11 limits the adenovirus to Ad5 dl331, which has a defective VAI but not a defective VAII gene, as disclosed in the specification, e.g. page 20, lines 25-26.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New matter. Claim 11 was added 10/22/2003 during examination of PCT/ES03/00140, and thus is not part of the originally filed application. Claim 11 is directed to an embodiment of

claim 1, which requires that both VAI and VAII genes be defective, wherein the adenovirus is dl331, which has a defective VAI gene but wild-type VAII gene. Thus, this claim either is outside the scope of claim 1, as indicated in the objection to claim 11 above, or the claim requires a descendent of dl331 in which the VAII gene is made defective. The latter constitutes impermissible new matter. There is no clear support for an embodiment of the method of claim 1 wherein the adenovirus used is a descendent from dl331 in which the VAII gene is made defective.

Lack of adequate written description. Claim 3 requires the adenovirus to have "a mutation in the sequences of the genes that control the expression of the VAI and VAII RNA genes". The specification does not explicitly identify any such genes, nor any such mutations that would cause the adenovirus to be "defective in its VAI and VAII virus-associated RNAs," as required by claim 1. The specification (page 5, lines 16-23) does teach that E1a controls expression of the remaining adenoviral genes, and teaches mutations in the coding sequence for E1a or in the promoter for E1a (replacement with tumor selective promoter) that would implicitly meet the limitation of this claim. However, these embodiments are not commensurate in scope with the breadth of the claim, since no other adenoviral genes that control expression of the VA RNAs are identified, nor is there any evidence that they were known by Applicant. Consequently, there is no evidence that Applicant was in possession of the genus of embodiments represented by this claim. This claim should be limited to mutations in E1a or its promoter that result in selective replication in tumor cells. However, as indicated below.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating "cancer" resulting from human tumor cells by administering an adenovirus that selectively replicates in the human cancer cells, wherein the adenovirus is descendent from a human adenovirus having a VAI gene and a VAII gene by mutation of the VAI and VAII genes such that the genes are inactivated and the human tumor cells have a constitutively active Ras pathway or are unresponsive to exposure to interferons, and wherein the adenovirus may additionally have mutations in E1a or E1b genes that result in further selective replication in tumor cells or have promoters operably linked to E1a, E1b or E4 that result in further selective replication in tumor cells, does not reasonably provide enablement for any other embodiments readable on the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-8 broadly embrace any adenovirus found in any host organism. The specification describes human adenoviruses, and teaches that not all serotypes even have VAI or VAII genes, but instead have a single VA gene. Human adenovirus of serotypes 11, 12, 14, 18, 31, 34, 35, 40 and 41 and simian adenovirus 7 do not have VAI and VAII genes, but rather a single VA gene (see Table 2 of Ma et al., J. Virol. 70: 5083-5099, 1996). Canine adenoviruses CAd1 and CAd2 have no VA genes at all (Abstract for Zhao et al., Bingdu Xuebo 13(1): 54-58, 1997). The specification does not teach how to render an adenovirus defective in its VAI and VAII genes when the adenovirus does not have endogenous VAI and VAII genes, and does not teach adenovirus other than human adenoviruses that have endogenous VAI and VAII genes.

This part of the rejection would be overcome by limiting the adenovirus to human adenovirus having endogenous VAI and VAII genes that have been inactivated.

Claims 1-3 do not require the adenovirus to be able to replicate in tumor cells, i.e. these claims read on fully replication defective adenovirus that lack E1a or lack any adenoviral structural genes, for example. Claims 4, 5 and 7-11 require the adenovirus to replicate selectively in tumor cells, but do not limit the types of tumor cells. However, the invention as described in the specification is directed solely to adenovirus that selectively replicate in certain tumor cells and subsequently kill them, specifically those types of tumor cells that have a constitutively active Ras, i.e. a Ras oncogene, or are non-responsive to interferon. The basis for the invention is that an adenovirus lacking the VAI and VAII RNAs will propagate in, and subsequently kill, tumor cells having a constitutively active Ras pathway or that are unresponsive to exposure to interferons, but will replicate poorly or not at all in normal cells. A human adenovirus that that is defective for VAI (or VA for adenovirus having a single VA gene) is able to replicate in these types of tumor cells because the cellular antiviral defenses mediated by PKR, the target of the VA RNA, is inactive in these types of tumor cells. There is no guidance for use of adenovirus for treating cancer where the adenovirus does not replicate in these two types of tumor cells (e.g. replication defective adenovirus) or will not replicate in tumor cells having a normal ras pathway or that is responsive to interferons. Thus, the guidance and examples in the specification is not commensurate in scope with the claimed subject matter.

Claim 4 is unclear, as indicated below, but it appears it is intended to limit the adenovirus to those also having mutations in E1a, E1b, or E4 that further restrict the types of tumor cells in which the adenovirus will replicate among those types of tumor that have a constitutively active

ras pathway or are responsive to interferon exposure. Mutations in E1a that confer selective replication in tumor cells that lack Rb and mutations in the E1b region that confer selective replication in tumor cells that lack p53 were known. Also known in the prior art were mutations in the promoters of the E1a, E1b, and E4 regions involving replacement of the endogenous promoters with promoters that are selectively active in tumor cells, and therefor that confer selective replication in tumor cells The specification mentions these types of mutations that confer selective replication in tumor cells beyond that conferred by the mutation of VA genes. However, the specification does not teach mutations in E4 genes that confer selective replication of an adenovirus in tumors. Nor is there any evidence of record that any such mutations were known in the prior art.

Consequently, in view of the limited guidance in the specification when compared to the breadth of the claims as to the types of adenovirus that can be made and used in treating cancer, the types of cancers cells the method would be effective for, and the additional modifications that can be made to the adenovirus, it would require undue experimentation to practice the invention as broadly as it is claimed. The specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991).

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are an individual, e.g. human, having a cancer to be treated and to which the adenovirus is administered. The claim as written merely requires administering the adenovirus without specifying what the adenovirus is administered to.

Claim 4 is unclear for recitation of "said adenovirus has mutations in the VA RNA genes in one or more genes of the group Ela, Elb, and E4". The VA genes are not located in any of the E1a, E1b, or E4 genes, so it is unclear what the limitation is directed to. If the claim was intended to indicate that the in addition to the mutations in the VA RNA genes, the adenovirus also has mutations in one or more genes of the E1a, E1b, and E4 regions, then insertion of --and-- after "VA RNA genes" would be remedial. However, such an amendment would then raise the issue of which preceding limitation "to obtain selective replication in tumors" refers, the mutations in the "VA RNA genes", "the mutations in one or more genes of the group E1a, E1b, and E4", or something else.

Regarding claim 8, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The metes and bounds of claim 9 are unclear for recitation of "a human adenovirus derived from a serotype between 1 and 50" (emphasis added). It is unclear if the claim is directed to human adenovirus of serotypes 1 through 50 or of serotypes 2 through 49.

As indicated in the objection to claims 9 and 11 above, some of the adenoviruses described in these claims fall outside the scope of claim 1, which requires a defective VAI gene

and a defective VAII gene, because they either have a single endogenous VA gene, and thus no VAI or VAII gene (claim 9) or because the adenovirus has an endogenous VAII gene that is not defective (dl331 of claim 11). Consequently, the metes and bounds of these claims is unclear. For claim 9, it is unclear whether the claim embraces the use of mutants of only those human adenovirus serotypes that have endogenous VAI and VAII genes, and excludes serotypes 11, 12, 14, 18, 31, 34, 35, 40 and 41 for example, or whether as it appears the claim also embraces adenovirus made from a parent adenovirus having only a single VA gene in nature by rendering the single VA gene defective. In the case of claim 11, it is unclear if the claim requires dl331, as it recites, or whether the claim actually requires a descendent of dl331 in which the VAII gene has also been made defective.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Little et al., US 6,254,862.

Little discloses a method for treating cancer by administering to a cancer patient an adenovirus having the E1a genes of the adenovirus replaced with a promoter of an alpha-fetoprotein gene in order to limit replication of the adenovirus to tumor cells in which the promoter is active. See entire reference, especially claims 1 and 37. As disclosed in the instant specification (page 5, lines 16-23), the E1a region controls expression of the remaining adenoviral genes, and therefore expression of the VAI and VAII genes. Since this adenovirus is defective for expression of the E1a region in normal adult human cells because of the replacement of the E1a promoter with the alpha-fetoprotein gene promoter, its expression of VAI and VAII RNAs is defective and consequently the level if VA RNAs is defective. Thus, the adenovirus inherently meets the limitations of claims 1 and 3.

This rejection would be overcome by amending the claims to limiting the adenovirus to one where the VAI and VAII genes were mutated such that functional VAI and VAII RNAs are not produced.

Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Kuo et al., US 2004/0132675.

Kuo discloses a method for treating cancer comprising administering a gutless adenovirus vector comprising a gene encoding a soluble Flk1/KDR receptor, which leads to inhibition of angiogenesis. Since the gutless adenovirus has been deleted of all adenoviral coding regions, it has mutations in both VAI and VAII genes, as well as the genes that control expression of VAI and VAII, whatever they happen to be. Consequently, the adenovirus is defective for both of its VA RNAs. See entire reference, especially ¶¶ 0023-0026 and claims 1, 4, and 7-11.

Claims 1-3 do not require that the adenovirus be able to replicate in tumor cells. This rejection would be overcome by amending the claims to limiting the adenovirus to one which selectively replicates in tumor cells that have a constitutively active ras pathway or that are unresponsive to exposure to interferons.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Coffey et al., WO 01/35970, in view of Thimmappaya et al. (Cell 31: 543-551, 1982). This rejection is necessitated by the uncertainty of whether the adenovirus in claim 11 is dl331 itself or a dl331 in which the VAII gene has also been made defective. The rejection is directed to the first possibility.

Coffey teaches a method for treating cancer characterized by tumor cells having an activated (constitutively active) Ras pathway by administering to the cancer patient an adenovirus having an inactivated VAI gene. This adenovirus will replicate in such tumor cells, but not normal cells, and lyse them. Coffey does not teach that Ad5 dl331 specifically should be used.

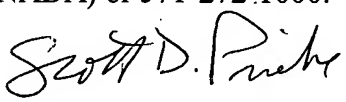
However, Thimmappaya et al. (Cell 31: 543-551, 1982) describes Ad5 dl331, which is a human Ad5 carrying a deletion in VAI, which replicates poorly in normal cells (see entire document, especially page 543, col. 2; page 549, bridging cols. 1-2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have used dl331 of Thimmappaya in the method of Coffey, since dl331 was a known replication competent (albeit poorly) adenovirus deficient in VAI, and one of skill in this art would have looked to the prior art for the type of adenovirus required by the method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Scott D. Priebe, Ph.D.
Primary Examiner
Art Unit 1633